THE EFFECTS OF EPINEPHRINE AND EPHEDRINE ADMINISTERED INTRATHECALLY UPON CARDIAC AUTOMATICITY DURING CYCLOPROPANE ANESTHESIA * †

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THE desire to prolong the duration of spinal anesthesia by combining vasoconstrictors with the anesthetic agent has been a recent revival in anesthesiology. Recently Bray, Katz and Adriani (1) performed a controlled study in man using epinephrine, ephedrine, neosynephrin and oenethyl in combination with pontocaine and nupercaine. They found epinephrine to be the most efficient for prolonging anesthesia. The use of epinephrine to prolong spinal anesthesia may be justified and is becoming widespread. Although ephedrine is not as effective as epinephrine, it is nevertheless used by many clinicians. Frequently it is desirable or necessary to supplement spinal anesthesia with an inhalation anesthetic. Not infrequently cyclopropane is selected because of its rapidity of action. It is well recognized in certain instances that vasoconstrictors topically, intravenously, intramuscularly and subcutaneously may cause untoward side effects when used with inhalation anesthesia. Whether or not similar effects are produced when the drugs are administered intrathecally has not been determined.

It is a well established fact that cyclopropane increases the irritability of the automatic tissues of the heart. It is further recognized that epinephrine behaves in a similar fashion. Meek et al. (2) have studied cardiac irregularities induced by amines possessing vasopressor activity during cyclopropane anesthesia. They studied the effects of epinephrine in the unanesthetized dogs and determined the average dose which produced arrhythmias. Reflex vagal inhibition of the pacemaker with or without escape of the A–V node, bundle or ventricles was the most frequent disturbance in rhythm. Tachycardia or fibrillation was uncommon when this dose was administered. The same dose of epinephrine caused serious cardiac arrhythmias when the dogs were

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deeply anesthetized with cyclopropane. They demonstrated that as little as 0.01 mg. of epinephrine per kilogram of body weight in 5 cc. of physiologic saline solution given intravenously at a rate of 1 cc. every ten seconds during deep cyclopropane anesthesia caused ventricular fibrillation and death. Inasmuch as so little epinephrine in combination with cyclopropane causes serious circulatory disturbances, it becomes important to know whether or not the passage of epinephrine from the subarachnoid space into the general circulation is sufficiently rapid to be hazardous if spinal anesthesia is supplemented or combined with cyclopropane. Likewise, Meek et al. (6) have shown that ephedrine administered during cyclopropane anesthesia in dogs also causes arrhythmias. Apparently these arrythmias are not as severe as those caused by epinephrine. Small doses cause bradycardia. Most serious cardiac irregularities occur when larger doses are used. The response is variable and is influenced considerably by the depth of anesthesia and dosage used. As in the case of epinephrine the response following intrathecal administration during cyclopropane anesthesia becomes of interest.

METHOD

Ten dogs were studied. Continuous electrocardiographic observations and serial electrocardiograms were taken, using standard Lead

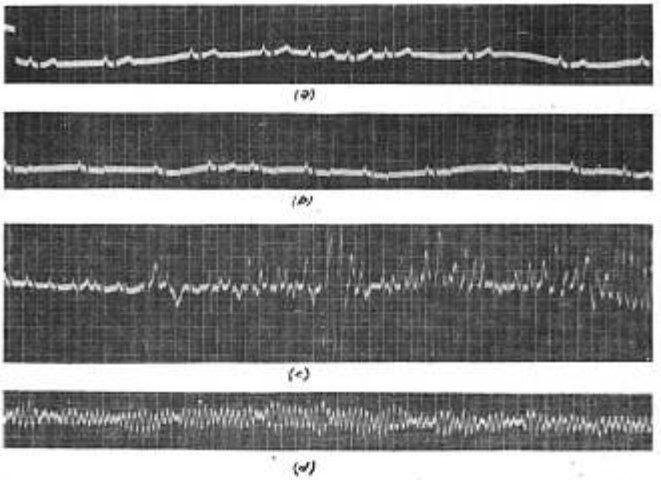

FIG. 1. (a) Control, dog 4. Pentobarbital and cyclopropane anesthesia using lead II. (b) Tracing after injection of 1 mg. of epinephrine intrathecally. (c) Tracing after intravenous injection of spinal fluid withdrawn one hour after the intrathecal injection. (d) Tracing shortly after tracing shown in III.

II. Six dogs were given 30 mg. of pentobarbital per kilogram of body weight to facilitate preparation and endotracheal intubation. No morphine or belladonna alkaloids were used. Cyclopropane anesthesia was induced and maintained in the third plane using the carbon dioxide absorption technic. Anesthesia was maintained for twenty minutes before any of the experiments were started.

The first 3 dogs (1, 2 and 3) were given a standard test dose (0.01 mg. of epinephrine per kilogram of body weight in 5 cc. of physiologic saline at rate of 0.1 cc.) after anesthesia was established as advocated by Meek and co-workers (6) until ventricular tachycardia occurred. After the rhythm had returned to normal, 1 mg. of epineph-

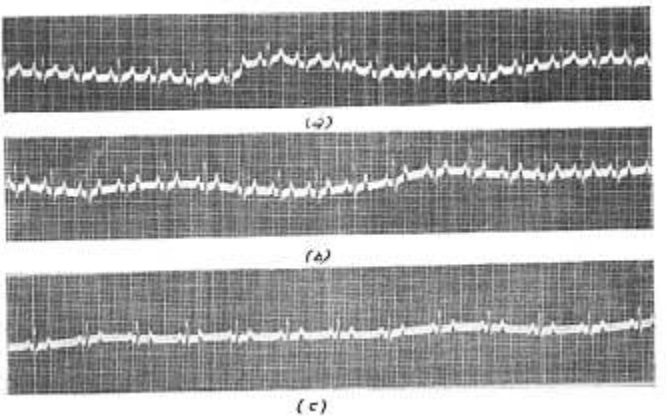

FIG. 2. (a) Control dog 10. Cyclopropane anesthesia using Lead II. (b) Tracing immediately after injection of 50 mg. of ephedrine intrathecally. (c) Tracing immediately after intravenous injection of spinal fluid withdrawn one hour after intrathecal injection of ephedrine.

rine (1:1000) was administered intrathecally. One milligram of epinephrine is the upper limit of the dose usually employed clinically in man for spinal anesthesia. In a dog, therefore, this dose is far in excess of that used clinically in man. Continuous electrocardiographic observations were made during the ensuing hour. Anesthesia was maintained in the third plane of the third stage as evidenced by loss of intercostal activity. At the end of the hour the standard test dose of epinephrine was again repeated intravenously to be certain that the heart was still sensitized to the combination.

One dog, (number 2) was treated as the others except that at the end of one hour 2 mg. of epinephrine was injected intrathecally instead of the intravenous test dose. After the second hour an additional 5

mg. was administered intrathecally. At the end of the third hour the standard test dose of epinephrine was administered intravenously.

In two dogs (numbers 4 and 5) spinal fluid was withdrawn after one hour and 0.5 cc., undiluted, was administered intravenously in lieu of the standard test dose to observe whether or not epinephrine was still present in appreciable quantities in the subarachnoid space.

In one dog (number 6), 1 mg. of epinephrine was injected into the intraspinous ligaments instead of intrathecally to observe the effect and the rapidity of local absorption of epinephrine upon cardiac rhythm.

In two dogs (numbers 7 and 8) a trephine was performed and 1 mg. of epinephrine was injected into the ventricle instead of into the spinal subarachnoid space.

Two dogs (numbers 9 and 10) were anesthetized with cyclopropane anesthesia without barbiturate and maintained in the third plane anesthesia. The barbiturate was omitted because it affords protective action for the heart from arrhythmia caused by ephedrine. Fifty milligrams of ephedrine, the upper limit of the dose used clinically in man, was injected intrathecally. The dogs were then observed electrocardiographically for one hour, at the end of which time 1 mg. of ephedrine per kilogram of body weight was administered intravenously.

Determinations of alveolar or blood concentrations of cyclopropane were not made. Blood pressure was not studied.

RESULTS

Results are summarized in table 1. Dog 1 developed a ventricular tachycardia after having been given 1 cc. of the intravenous test dose of epinephrine. The arrhythmia was allowed to disappear. When normal rhythm was reestablished 1 mg. of epinephrine was introduced intrathecally. No change in cardiac rhythm was noted during the ensuing hour of cyclopropane anesthesia. Upon repeating the test dose intravenously (1.2 cc.) ventricular fibrillation developed and the dog died in less than one minute. No attempts at defibrillation were made.

Dog 2 also developed ventricular tachycardia after 5 cc. of an intravenous test dose of epinephrine had been administered. The rhythm was allowed to return to normal. No changes in cardiac rhythm were noted during the first hour following the introduction of 1 mg. of epinephrine intrathecally or during the second hour following the injection of 2 mg. During the third hour after 5 mg. was introduced intrathecally (a total of 8 mg. intrathecally for the entire experiment) paroxysms of ventricular tachycardia were noted eighty-eight seconds after the injection. The rhythm returned to normal within ten minutes. Four cubic centimeters of the test dose of epinephrine was then administered intravenously. Ventricular premature beats were observed but ventricular tachycardia did not develop. The animal survived.

Dog 4 behaved in a similar manner to the first 3 dogs. One milligram of epinephrine intrathecally caused no arrhythmias during one hour of third plane of anesthesia. At the end of the hour 0.5 cc. of spinal fluid was withdrawn and injected intravenously. Ventricular tachycardia developed. This was followed by ventricular fibrillation and death of the animal.

Dog 5 was treated and behaved similarly to dog 4. Spinal fluid, 0.5 cc., withdrawn and administered intravenously after one hour of anesthesia likewise caused paroxysms of ventricular tachycardia which were followed by ventricular fibrillation fifteen seconds later and death of the animal. Apparently considerable epinephrine was still present in the spinal fluid even though an hour had elapsed after the injection. Spinal fluid withdrawn prior to the administration of epinephrine intrathecally did not cause any change in rhythm when injected into the vein during cyclopropane anesthesia.

The effects of epinephrine injected inadvertently into the intraspinous ligaments instead of intrathecally were observed in dog 6. A–V nodal rhythm and ventricular premature beats appeared within

TABLE 1

Dog	Drug	Route Given	Dosage	Arrhythmia Produced	Onset, *seconds*	Duration of Effect, *seconds*
1	Epinephrine	Intravenous	0.034 mg. (1 cc.)	(1) Frequent Ventricular Premature Beats	27.2	10.0
				(2) Ventricular-Tachycardia	37.2	46.0
				(3) Frequent Ventricular Premature Beats	85.2	22.0
		Intraspinous	1 mg. (1 cc.)	None		
		Intravenous	0.041 mg. (1.2 cc.)	(1) Ventricular Premature Beats	25.7	3.4
				(2) Ventricular Fibrillation	29.1	Died
2	Epinephrine	Intravenous	0.08 mg.	(1) Ventricular Premature Beats	15.0	3.6
				(2) Ventricular Tachycardia	18.6	74.4
				(3) Ventricular Premature Beats	93.2	4.8
		Intrathecal	1 mg. (1 cc.)	None	—	—
			2 mg. (2 cc.)	None	—	—
			5 mg. (5 cc.)	(1) A.V. Nodal Rhythm	54.0	35.2
				(2) Frequent Ventricular Premature Beats	58.0	27.2
				(3) Paroxysms of Ventricular Tachycardia	88.8	4.4–4.8–2.4
				(4) Frequent Ventricular Premature Beats	139.2	54.8
		Intravenous	0.06 mg. (4 cc.)	(1) A.V. Nodal Rhythm	27.6	14.4
				(2) Frequent Ventricular Premature Beats	29.4	36.4
3	Epinephrine	Intraspinous	1 mg. (1 cc.)	None	—	—
		Intravenous	0.044 mg. (2 cc.)	(1) Occasional Ventricular Premature Beats	10.8	19.2
				(2) Frequent Ventricular Premature Beats	30.0	64.0

TABLE 1 (*continued*)

Dog	Drug	Route Given	Dosage	Arrhythmia Produced	Onset, *seconds*	Duration of Effect, *seconds*
4	Epinephrine	Intrathecally	1 mg. (1 cc.)	(1) Frequent Ventricular Premature Beats	12.8	5.4
		Intravenous	0.5 cc. Spinal	(2) Ventricular Tachycardia	18.2	6.4
		Spinal Fluid	Fluid 1 hour after 1 mg.	(3) Frequent Ventricular Premature Beats	24.6	4.0
			Intraspinous	(4) Occasional Ventricular Premature Beats	25.0	48.4
				(5) Electrical Alternation	73.4	36.0
5	Epinephrine	Intrathecally	1 mg. (1 cc.)	None	—	—
		Intravenous	0.5 cc. Spinal	(1) Ventricular Premature Beats	8.4	3.4
		Spinal Fluid	Fluid 1 hour after 1 mg.	(2) Paroxysms-Ventricular Tachycardia	11.8	1.4–0.8
			Intraspinous	(3) Ventricular Fibrillation	15.6	Expired
6	Epinephrine	Into Spinous Ligament	1 mg. (1 cc.)	Ventricular Fibrillation	15	Expired
7	Epinephrine	Intraventrically	1 mg.	None	—	—
8	Epinephrine	Intraventricular	1 mg.	None	—	—
		Intravenous Cerebrospinal Fluid		Fleeting Ventricular Tachycardia	14	60
9	Ephedrine	Intrathecally	50 mg.	None	—	—
		Intrathecally Spinal Fluid		Bradycardia	15	—
10	Ephedrine	Intrathecally Intravenously	50 mg.	None	—	—
				Bradycardia	15	—
				Ventricular Premature Beats		

thirty seconds after 1 mg. of epinephrine was introduced at this site. Apparently absorption is sufficiently rapid from the intraspinous tissue to be a hazard during cyclopropane anesthesia. It was thought that these observations on the one dog were sufficient because the response obtained merely confirms previously reported observations by others workers.

The mode of elimination of drugs and other substances from the subarachnoid space has not been clearly defined. It has been assumed that the drug remains in the thoracolumbar sacral portion of the subarachnoid space in spinal anesthesia. The possibility that epinephrine is more rapidly absorbed in the event it passes into the ventricles was explored by the experiments performed on dogs 7 and 8. One milligram of epinephrine was injected into the ventricle after trephining

the skull. No significant disturbances in rhythm were noted over a one hour period. After one hour, 1 cc. of the spinal fluid was withdrawn from the ventricle of dog 8 and injected intravenously. Because of technical difficulties, none was obtained from dog 7. A fleeting wave of paroxysmal tachycardia lasting several seconds occurred, but the response was nowhere near as pronounced as the injection of spinal fluid from the lumbar region (dogs 4 and 5).

The effects of ephedrine were studied in dogs 9 and 10. Fifty milligrams of ephedrine administered intrathecally caused no changes in rate or rhythm during the hour following the injection. Fifty milligrams is the upper limit of the dose employed clinically for man. As in previous experiments cyclopropane anesthesia was maintained in third plane. One hour after the intrathecal injection, 1 mg. of ephedrine per kilogram of body weight was administered intravenously. A slowing in rate from 125 to 98 appeared two and one-half seconds after injection (dog 9). Dog 10 behaved similarly. Ventricular tachycardia, fibrillation and othe disturbances of rhythm characteristic of the epinephrine combination were not observed.

DISCUSSION

The rapidity of passage of drugs from the subarachnoid space in a situation such as this is a factor of utmost clinical importance. The foregoing data indicate that epinephrine disappears slowly from the spinal subarachnoid space. This is not in agreement with current thought and teaching. Best and Taylor (3) stated that true solutions pass readily through the arachnoid villus. Colloids pass through more slowly depending upon the size of the molecule. Presumably, most of the absorption from the subarachnoid space occurs within the cranium. Some absorption occurs in the spinal canal by way of the lymphatics along the spinal cord. Absorption is facilitated by the circulation of the cerebrospinal fluid which is from the cranium to the cord and back to the cranium.

There is also other evidence that drugs do not readily pass from the intrathecal space into the blood stream. In a series of approximately 210 cases of spinal anesthesia, Bray, Katz and Adriani (1) observed no significant alterations in blood pressure when epinephrine, neosynephrin, ephedrine and oenethyl were administered intrathecally in therapeutic doses in man. Similar quantities of the same drug intravenously cause notable changes in blood pressure in man. Bullock and MacDonald (4) have reported that procaine diffuses slowly from the intrathecal space in cats. Weiland, Broh-Kahn and Mirsky (5) have reported that concentrations of glucose injected into the subarachnoid space remained elevated for periods of one hour or more after injection. There was no hyperglycemia or other evidence of rapid passage of the glucose into the blood stream.

Apparently epinephrine and ephedrine behave like glucose and procaine and pass slowly from the subarachnoid space. The absence of cardiac effects in dogs and the absence of pressor effects in clinical cases suggest slow passage from the spinal canal into the vascular system in both man and dog. The continued presence of epinephrine in cerebrospinal fluid after one hour suggests absence or a low concentration of the enzymes which are normally present in other body fluids which detoxify epinephrine.

SUMMARY AND CONCLUSIONS

The effects of epinephrine and ephedrine administered intrathecally upon cardiac automaticity during cyclopropane anesthesia were studied in 10 dogs. Continuous electrocardiographic observations were made on cardiac rate and rhythm for one hour after injection of the vasoconstrictor substance. The characteristic disturbances in cardiac rhythm which occur after epinephrine is administered intravenously were not observed when the drug was administered intrathecally. Ephedrine likewise caused no changes in cardiac rhythm. At the end of one hour epinephrine was still present in sufficient quantities in cerebrospinal fluid to cause severe disturbances in cardiac rhythm and even death when withdrawn and administered intravenously.

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